REMARKS

I. Status of Claims

Claims 1-5, 11-14, 19, 21-26, and 33-41 are pending.

Claims 19, 25, and 33-41 stand withdrawn from consideration as drawn to a non-elected invention. Applicants again note that claims 37-41 are process claims which depend from elected product claims. Upon finding the product claims allowable, Applicants respectfully request that the Office rejoin and fully examine method claims 37-41, as required by rejoinder practice under M.P.E.P. § 821.04.

Claims 1-5, 11-14, 21-24 and 26 are under consideration. Applicants acknowledge with appreciation that the Office has withdrawn all previous rejections in this application. Office Action, pages 2-4.

II. Rejections Under 35 U.S.C. § 103(a)

Before addressing the rejections under 35 U.S.C. § 103(a), Applicants respectfully note that while the current Office Action is non-final, it has required Applicants to incur additional expenses that could have been avoided by presenting these rejections in the initial Office Action. M.P.E.P. § 707.07(g) directs the Office to avoid piecemeal examination as much as possible. Here, there does not appear to be any reason why the multiple combination of references relied upon in the newly added rejections could not have been presented in the previous Office Action. In particular, the EV71 IRES was recited in the original claims. As discussed in M.P.E.P. § 904.03, that particular IRES should have been included in the Office's initial search and, if appropriate, addressed in the initial Office Action.

A. Finkelstein in view of McMinn

The Office rejects claims 1-5, 11-13, 21, 24 and 26 under 35 U.S.C. § 103(a) as allegedly unpatentable over the combination of Finkelstein *et al.*, J. Biotechnol. Vol. 75, pp. 33-44 (1999) ("Finkelstein") and McMinn, FEMS Microbiology Reviews Vol. 26, pp. 91-107 (2002) ("McMinn"). Office Action, page 5.

According to the Office, "Finkelstein et al teaches a bicistronic baculovirus vector that comprises a baculovirus polyhedrin promoter (Ppol) and an EMCV IRES separating two reporter genes such as chloramphenicol transferase (CAT) and firefly luciferase (LUC) and recombinant baculoviruses." *Id.* The Office acknowledges that Finkelstein does not teach using the EV71 IRES in a dicistronic baculovirus vector. *Id.* at 6. It takes the position, however, that because McMinn teaches that EV71 contains an IRES that can be substituted for the PV1(M) IRES, it would have been obvious to substitute the EV71 IRES in the baculovirus vector of Finkelstein. *Id.* Applicants respectfully traverse the Office's position because the Office has not established a *prima facie* case of obviousness.

1. No Motivation Exists To Combine Finkelstein And McMinn

"The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness." M.P.E.P. § 2142. The *prima facie* case of obviousness must meet several essential criteria, including providing some reason, suggestion, or motivation in the prior art to lead one of ordinary skill in the art to combine the teachings of the references in the manner proposed by the Office. M.P.E.P. § 2143. That suggestion or motivation must be found in the prior art, not in Applicant's disclosure. *Id.*

"The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." M.P.E.P. § 2143.01 (citing *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990)). Thus, without a clear and particular reason to combine or modify the teachings of the references, the identification of the individual elements of a claimed invention in the prior art is not sufficient to negate patentability. *See, e.g., In re Rouffet*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1457 (Fed. Cir. 1998). In *Rouffet*, the Federal Circuit observed that "virtually all [inventions] are combinations of old elements" and stated that "the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *Id.*, 47 U.S.P.Q.2d at 1457.

Applicants respectfully submit that there is nothing in the teachings of Finkelstein or McMinn, either alone or in combination, that would have motivated the ordinary artisan to substitute McMinn's EV71 IRES for the EMCV IRES used by Finkelstein. The Office states that:

> One would have been motivated to [modify the teachings of Finkelstein by using the EV71 IRES] in order to receive the expected benefit, as suggested by McMinn, of obtaining more efficient expression of two cistrons separated by an EV71 IRES in a baculovirus expression system."

Office Action, page 6. While Finkelstein does indicate that the EMCV IRES used in its bicistronic baculovirus vector was not as efficient in insect cells as in mammalian cells, Finkelstein theorizes that the low levels of expression from the EMCV IRES is either due to low levels of factors essential for IRES activity in insect cells or due to low affinity

of the insect cell factors for the EMCV-IRES. Finkelstein, page 43, concluding remarks. Finkelstein suggests that the low level of expression is due to features of the insect cells, not the IRES used, and so provides no motivation to select a different IRES.

McMinn does not teach, nor does it any way suggest, that the EV71 IRES would provide more efficient expression than the EMCV IRES in any cell type, let alone insect cells. Instead, McMinn teaches only that substitution of the EV71 IRES for the IRES in the PV1(M) poliovirus does not reduce the neurovirulence of PV1(M). McMinn, page 102, first paragraph. McMinn does not evaluate or speculate about the efficiency of the EV71 IRES in supporting internal ribosome entry in any cell type, and McMinn does not compare the EV71 IRES to the EMCV IRES. Accordingly, Applicants respectfully submit that McMinn does not teach or suggest that the EV71 IRES would be desirable to use in a bicistronic vector in general, or that it is a more desirable IRES than the EMCV IRES.

The Office's reliance upon McMinn's teaching that an IRES exists in EV71 is thus nothing more than the identification of an element of Applicants' invention that the Office then suggests, in hindsight, could potentially be substituted into the bicistronic vector of Finkelstein. But there is no teaching or suggestion in either reference of the desirability of this substitution. When the references fail to suggest the desirability of their combination, the burden is on the Office to provide "a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." M.P.E.P. § 2142. Further, "[c]onclusory statements of similarity or motivation, without any articulated rationale or evidentiary support, do not constitute sufficient factual findings." M.P.E.P. § 2144.08. Here, for the reasons noted,

the statement of motivation provided is not supported by either a convincing line of reasoning or evidentiary support. Accordingly, Applicants respectfully submit that the Office has not established that the ordinary artisan would have been motivated to make the proposed substitution and so has failed to establish a *prima facie* case. The rejection should be withdrawn for at least this reason.

2. McMinn Does Not Provide A Reasonable Expectation That The EV71 IRES Would Function In A Dicistronic Expression Vector

A *prima facie* case of obviousness also requires that the references relied upon provide a reasonable expectation that their teachings could be successfully combined or modified in the manner proposed by the Office. M.P.E.P. § 2143.02. It is impermissible to rely upon an applicant's disclosure to show, in hindsight, that a combination of elements functions for the intended purpose; instead, the reasonable expectation of success must come from the references' teachings. *See, e.g., Noelle v. Lederman*, 355 F.3d 1343, 1352, 69 U.S.P.Q.2d 1508, 1515-16 (Fed. Cir. 2004).

McMinn, either alone or in combination with Finkelstein, does not provide a reasonable expectation that the EV71 IRES would function as an IRES in a dicistronic expression vector. In particular, McMinn does not directly show that the EV71 IRES functions to permit internal ribosome entry for protein expression. Instead, McMinn only teaches that substitution of the EV71 IRES for the IRES in the PV1(M) poliovirus does not reduce neurovirulence of PV1(M). McMinn, page 102, first paragraph. Further, McMinn uses chimeric virus comprising the EV71 IRES, not a bicistronic vector. The Office alleges that, "[a]bsent . . . evidence to the contrary, there would have been a reasonable expectation in using the EV71 IRES because others have successfully used

an IRES in dicistronic vectors." Finkelstein, however, teaches that IRES activity in one vector system does not provide a reasonable expectation that the IRES will be efficient, or even functional, in other expression systems. Thus, even had McMinn shown efficient EV71 IRES activity from a bicistronic vector in poliovirus, those results would not provide a reasonable expectation that the EV71 IRES would function in the baculovirus system as part of a bicistronic vector.

Because the Office has provided neither a reasonable expectation of success nor motivation based on the teachings of Finkelstein and McMinn, the Office has not established a *prima facie* case of obviousness. Accordingly, Applicants respectfully request the Office to withdraw the rejection.

B. Finkelstein and McMinn in view of Urabe

The Office also rejects claims 1-5, 11-13, 21-24 and 26 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Finkelstein and McMinn in further view of Urabe *et al.*, Gene, Vol. 200, pp. 157-62 (1997) ("Urabe"). Office Action, pages 6-7. In this rejection, the Office relies upon the teachings of Finkelstein and McMinn as discussed above, but recognizes that those references fail to teach a bicistronic vector in which one of the cistrons comprises a therapeutic gene. *Id.* at 7. According to the Office, however, Urabe teaches that either an HCV or EMCV IRES can be used in a dicistronic adeno-associated viral (AAV) vector that contains a therapeutic gene. *Id.* In view of those teachings, the Office takes the position that one of ordinary skill in the art would have found it obvious to modify the combined teachings of Finkelstein and McMinn to produce a vector that expresses a therapeutic gene in baculovirus. *Id.*

Applicants traverse the Office's position. As discussed *supra* in subsection (A), Finkelstein in view of McMinn does not provide the ordinary artisan with the motivation to use the EV71 IRES in a bicistronic vector for baculovirus. Neither do those references provide a reasonable expectation that the EV71 IRES would successfully function in such a vector. The teaching of Urabe that an IRES can be used to express a therapeutic gene, when considered with the primary references, does nothing to remedy these deficiencies in Finkelstein and McMinn. Accordingly, Applicants respectfully request that the Office also withdraw this rejection.

C. Urabe in view of McMinn

Claims 1-5, 11, and 13 also stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Urabe in view of McMinn. Office Action, page 7. Urabe is again relied upon for its teaching that either an HCV or EMCV IRES can be used in a dicistronic AAV vector. *Id.* at 8. The vector can contain either a therapeutic gene or a reporter gene, and can be expressed in mammalian cells. *Id.* The Office acknowledges that Urabe does not teach using the EV71 IRES in a dicistronic AAV vector. *Id.* It is the Office's position, however, that because McMinn teaches that EV71 contains an IRES that can be substituted for the PV1(M) IRES, it would have been obvious to substitute the EV71 IRES into the AAV vector of Urabe. *Id.* at 8-9

Applicants also traverse this rejection. As discussed *supra* in subsection (A), McMinn's teaching regarding the EV71 IRES does not provide a reasonable expectation that the EV71 IRES could be used successfully in a bicistronic vector. Urabe, which

does not mention the EV71 IRES, does not remedy this defect in the teachings of McMinn.

As with the combination of Finkelstein and McMinn, Applicants also respectfully submit that the ordinary artisan would not have been motivated to substitute the EV71 IRES of McMinn for the HCV IRES used in Urabe's vectors for expression of therapeutic genes in an adeno-associated virus system. In particular, Urabe emphasizes selection of the HCV IRES because it is small - only 230 nucleotides in length - and therefore permits the insertion of larger therapeutic genes into the vector. Urabe, page 158, first partial paragraph. In contrast, the 5'UTR containing the EV71 IRES, which is shown in Figure 1 of the Specification, is 663 nucleotides in length. The ordinary artisan, therefore, would not have been motivated to substitute the larger EV71 IRES for the smaller HCV IRES.

Because the references, considered either alone or in combination, do not provide the motivation to prepare a bicistronic vector comprising the EV71 IRES or a reasonable expectation that such a vector would function to express protein, the Office has failed to establish a *prima facie* case of obviousness. Applicants respectfully request that the Office therefore withdraw the rejection.

D. van Zonneveld in view of McMinn

The Office further rejects claims 1, 3-5, 11, and 13 under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 6,447,768 to van Zonneveld *et al.* ("van Zonneveld") in view of McMinn. Office Action, page 9. van Zonneveld is said to teach "a dicistronic adenoviral vector that comprises a CMV promoter, NO synthase cDNA,

IRES from EMCV and VEGF or FGF4 cDNA as the angiogenic factors and cells containing the adenoviral vector." *Id.* As with Finkelstein and Urabe, the Office concedes that van Zonneveld does not teach using the EV71 IRES in a dicistronic vector, but it asserts that it would have been obvious to substitute the EV71 IRES into the adenoviral vector of van Zonneveld in view of the teachings of McMinn. *Id.*

This rejection also fails to establish a *prima facie* case, and Applicants therefore traverse it. Like Finkelstein, van Zonneveld provides no teaching or suggestion that the EMCV IRES used in its bicistronic vector should be substituted. Instead, van Zonneveld's invention focuses on inducing or enhancing angiogenesis by gene therapy. *See* van Zonneveld, Abstract. The teachings of van Zonneveld do not suggest that the EMCV IRES should be replaced, and the Office has not provided any rationale for its proposed substitution beyond alleging that McMinn suggests that the EV71 IRES would provide efficient expression. As already discussed, McMinn's minimal teachings do not reasonably suggest that the EV71 IRES would lead to efficient expression in any bicistronic vector system.

For at least these reasons, Applicants respectfully submit that the Office has also failed to establish a *prima facie* case of obviousness based on the teachings of van Zonneveld and McMinn. Accordingly, the rejection should be withdrawn.

E. Whitley in view of McMinn

Claims 1, 3-5, 11, and 13 are also rejected under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent No. 6,764,675 to Whitley *et al.* ("Whitley") in view of McMinn. Office Action, page 10. The Office relies upon Whitley as teaching "a

dicistronic herpes simplex virus (HSV) vector that comprises an Egr-1 promoter, the p40 and p35 subunits of mIL-12 separated by an IRES from EMCV and mammalian cells containing the vector." *Id.* Here too, the Office acknowledges that the primary reference fails to teach the EV71 IRES, but it nevertheless maintains that it would have been obvious to modify the teachings of Whitely in view of the teachings of McMinn.

Applicants traversal regarding the teaching of McMinn has been discussed *supra*. Whitley teaches the construction of a vector for the expression of the two subunits of a cytokine, IL-12, following infection with HSV. The IRES used to express the p35 subunit of IL-12 is from a commercial construct. *E.g.*, Whitely, col. 7, lines 9-23. Applicants respectfully note that Whitely does not indicate that there is any reason to replace the commercial IRES with an IRES from another source. And, as already discussed, McMinn's minimal teachings do not reasonably suggest that the EV71 IRES would lead to efficient expression in any bicistronic vector system. Thus, like the other references relied upon in combination with McMinn, this combination also does not provide any motivation to make the substitution proposed by the Office.

Because there is neither motivation to replace the IRES used in Whitely's vectors with the EV71 IRES, nor a reasonable expectation that, were the substitution made the EV71 IRES would function, there is no *prima facie* case of obviousness based on the teachings of the references. Applicants respectfully request the Office to withdraw the rejection.

F. Agarwal in view of McMinn

Claims 1-5, 11, and 13 are also rejected under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent No. 6,194,212 to Agarwal *et al.* ("Agarwal") in view of McMinn. Office Action, page 11. The Office states that Agarwal teaches "a dicistronic retroviral vector comprising a retroviral promoter such as LTR and an IRES from EMCV separating the RevM10 gene and the marker gene Lyt-2 and cells containing the retroviral vector." *Id.* The Office admits that Agarwal does not teach using the EV71 IRES. *Id.* It is the Office's position, however, that because McMinn teaches that EV71 contains an IRES that can be substituted for the PV1(M) IRES, it would have been obvious to substitute the EV71 IRES into the retroviral vector of Agarwal. *Id.* at 12

As with the other rejections involving McMinn, this rejection is also traversed at least because McMinn does not provide a reasonable expectation that the EV71 IRES can be used in a dicistronic vector, and Agarwal does not remedy this defect. Further, Agarwal, like Whitely, raises no concerns regarding the expression obtained from its IRES containing vector. Thus, this reference, either by itself or in combination with the minimal teachings of McMinn, also fails to provide any reason to substitute the EV71 IRES of McMinn for the IRES used by Agarwal. As noted *supra*, the references must teach or suggest the desirability of the substitution, and here, once again, they do not.

Accordingly, there is neither motivation to replace the IRES used in the vectors of the primary reference with the EV71 IRES, nor a reasonable expectation that, were the substitution made, the EV71 IRES would function. Because the Office has not established a *prima facie* case of obviousness, Applicants respectfully request the Office to withdraw the rejection.

G. Seguela in view of McMinn

The Office further rejects claims 1, 3-5, 11, and 14 under 35 U.S.C. § 103(a) as unpatentable over Seguela *et al.* (US 2003/0219858) ("Seguela") in view of McMinn. Office Action, page 12. Seguela is said to teach "a bicistronic nucleic acid vector that comprises a CMV promoter and two nucleotide sequences encoding ASIC2A and ASIC3 polypeptides separated by an IRES from EMCV and E. coli cells containing the vector." *Id.* at 12-13. Seguela does not teach using an EV71 IRES, but the Office again points to the teachings of McMinn as rendering obvious the modification of the Seguela vector with the EV71 IRES. *Id.* at 13.

Applicants' respectfully traverse this rejection essentially for the reasons elaborated *supra* regarding the other combinations of references cited by the Office. Seguela, like Whitely, uses a commercial EMCV IRES to achieve simultaneous expression of two genes. *See*, Seguela, paragraph [0186]. Seguela, again like Whitely, provides no reason to replace the commercial IRES with an IRES from another source. Accordingly, for at least the reasons discussed with respect to the combination of Whitely and McMinn, the claimed invention is also not obvious over the combination of Seguela and McMinn. Applicants respectfully request the Office to withdraw this rejection.

H. Kirkegaard in view of McMinn

Claims 1-5, 11, and 13 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Kirkegaard et al. (US 2004/0052765) ("Kirkegaard") in view of McMinn. Office Action, page 13. The Office points to Kirkegaard as teaching a dicistronic vaccinia virus

vector comprising a poliovirus IRES separating coding sequences for poliovirus 3A and GFP. *Id.* at 14. Kirkegaard does not teach using an EV71 IRES in a biological vector, as the Office admits. *Id.* But, the Office again finds the teachings of McMinn sufficient to render obvious the substitution of the EV71 IRES into the poxvirus vector of Kirkegaard. *Id.*

Unlike the previous rejections, Kirkegaard uses a poliovirus IRES, which is the same type of IRES substituted by the EV71 IRES in the teachings of McMinn. The Office asserts that there would therefore have been a reasonable expectation that the EV71 IRES could be used because "poliovirus IRES and EV71 IRES appear to be interchangeable." *Id.* Regarding the motivation to make the proposed substitution, however, the Office continues to rely on the "expected benefit, as suggested by McMinn, P, of obtaining efficient expression of two cistrons in a vaccinia virus construct." *Id.*

Although McMinn does replace the PV1(M) poliovirus IRES with the EV71 IRES, Applicants respectfully submit that this simple substitution is not the functional equivalent of preparing a bicistronic expression vector because McMinn produced chimeric virus. McMinn did not directly assess the ability of the EV71 IRES to provide cap-independent expression of a protein, but instead assayed whether the substitution affected neurovirulence. McMinn, page 102. McMinn, therefore, does not provide a reasonable expectation that the EV71 IRES would function in the context of a bicistronic vector.

Further, as with the other reference combinations, the ordinary artisan would not have been motivated to substitute the EV71 IRES for the IRES used by Kirkegaard

because Kirkegaard does not suggest there are any problems with the poliovirus IRES. Nor do the teachings of McMinn suggest that the EV71 IRES is more desirable than the poliovirus IRES. Applicants again note that "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." M.P.E.P. § 2143.01 (citing *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990)).

At least because neither the references nor any rationale provided by the Office suggest the desirability of the combination, the Office has not met its burden of presenting a *prima facie* case of obviousness. Accordingly, Applicants also respectfully request the Office to withdraw this rejection.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Jessica H Roanic

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By: Reg No. 54,869 For:
Steven P. O'Connor
Reg. No. 41,225
(571) 203-2718